REMARKS

Claims 1-9, 19 and 20 are pending in the present application. Claims 9 and 19 are allowed, and claims 1-8 and 20 are rejected. Applicants have amended claims 1, 2, 4, 9, 19 and 20 primarily to correct minor grammatical and typographical errors and to provide clear antecedent basis for certain claim terms. No new matter has been added.

Rejections under 35 U.S.C. § 103

Claims 1-8 and 20 are rejected under 35 U.S.C. § 103(a) as unpatentable over Dornburg (U.S. Patent No. 5,869,331, "Dornburg"), Novotny *et al.* ("Immunology," pp. 449-458, in Molecular Biology and Biotechnology, 1995, "Novotny"), Colcher *et al.* (*J. Natl. Cancer Inst.*, 82:1191-1197, 1990, "Colcher") and June *et al.* (U.S. Patent No. 6,352,694, "June") (Office Action, page 3).

This ground for rejection is respectfully traversed. The cited references, even when considered together, cannot satisfy the legal standard for obviousness. We begin by reviewing that standard and then turn to the referenced teachings.

For obviousness: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. Moreover, the suggestion to make the claimed combination and the expectation of success must both be found in the prior art, not in Applicants' disclosure. MPEP at 2143, citing In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991).

According to the Examiner,

> Dornburg teaches a retroviral vector particles [*sic.*] having target cell specificity which comprises a retroviral vector having a targeting peptide fused to the envelope protein of the retroviral vector to form a targeting envelope....[T]o make a retroviral vector particle specific for a cell-type of interest, the viral receptor binding peptide may be replaced with an antigen binding site of an antibody molecule (see column 4, lines 25-34). (Office Action, page 4).

The Examiner also states that

> Colcher et al. teaches that the Mab B6.2 IgG, used by Dornburg above, was generated by the immunization of Balb/c mice with membrane-enriched fraction of a human breast tumor (see material and methods)....Novotny et al. teaches the standard step required for the production of single chain antibodies has become a standard technique in the art....June et al. teach various production methods for generating antibodies, the immunogen may be a purified protein or alternatively may simple [*sic.*] be a whole cell which expresses the surface protein of interest (see columns 21 and 22, especially column 22, lines 56-58). (Office Action, page 4).

The Examiner then concludes that the present invention is obvious over these references. For the reasons that follow, there is no *prima facie* case for obviousness.

A. No suggestion or motivation to combine the references

There is no suggestion in the references, or otherwise, that one of ordinary skill in the art should combine their teachings. Dornburg describes methods for generating only certain cell-specific retroviral vectors. The vectors include a targeting peptide, and one of the types of targeting peptides Dornburg suggested was "the antigen binding site of an antibody" (Abstract). The only examples Dornburg provided are of two previously cloned and well characterized scFvs: anti-DNP (see column 4, line 40) and B6.2scFv (column 7, line 34). Nothing in Dornburg suggests producing a single chain antibody (scFv) and then using that scFv to generate cell-specific retroviral vectors, as recited in the presently pending claims.

June teaches that an animal can be immunized with whole cells that express a protein of interest on their surface, and that the animal can produce antibodies in response. Colcher immunized mice with a membrane-enriched fraction of a human breast tumor and subsequently generated a monoclonal antibody. Novotny produced immune libraries by amplifying RNA from IgG-producing B cells. None of the teachings of these references extends beyond the field of immunology, and there is certainly no suggestion that one should generate scFvs as part of a method for producing cell-specific retroviral vectors, as Applicants now claim.

With all due respect, the Examiner's statements regarding the required motivation are conclusory statements. The Examiner simply asserts that "[o]ne having ordinary skill in the art

at the time the invention was made would have been motivated to use whole cells for the immunization step in animals because the use of whole cells requires less preparation of the antigen", and that "[o]ne having ordinary sill [*sic.*] in the art at the time would also recognize that injecting a whole cell in the animal allows for the production of antibodies that recognize not only the cell surface receptors but also see the receptor in context of other cell surface molecules" (Office Action, pages 5-6, emphasis added). However, the Federal Circuit has held that such conclusory statements do not adequately demonstrate a motivation to combine (*see* In re Lee, 277 F.3d 1338 (Fed. Cir. 2002)). Indeed, injecting whole cells may require less preparation than many other possible scenarios one might imagine, but that does not mean there was a motivation to include that step (or any other step) in the method now claimed.

Further, the Federal Circuit has held that "[c]ombining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight." (In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999), quoting Interconnect Planning Corp. v. Feil, 774 F.2d 1132 (Fed. Cir. 1985)). Here, the Examiner briefly characterizes Dornburg, June, Colcher, and Novotny before indicating which of the two "parts," if you will, of Applicants' method is broadly disclosed in each: the retroviral "part" in Dornburg and the generation-of-scFv "part" in June, Colcher, and Novotny. As difficult as it may be, the Examiner must view the prior art as one of ordinary skill in the art would have viewed it at the time the present application was filed. It is impermissible to search out the steps of the presently claimed methods using the present disclosure as a guide; the Examiner cannot – with the present method now firmly in mind – simply piece together the prior art until all of the present steps are found. On this basis alone, the rejection based on "obviousness" should be withdrawn.

B. The combined references do not teach or suggest all the claim limitations

Even if, somehow, the references were to provide one of ordinary skill in the art with the requisite motivation, they fail to teach or suggest all of the claim limitations.

The presently pending claims are drawn to methods for producing cell-specific retroviral vectors. Claim 1 includes the steps of (1) immunizing a mammal with one or more cell

population(s); (2) isolating RNA from the immunized mammal, the RNA comprising RNA from a B cell; (3) producing, from the isolated RNA, cDNAs that encode single chain antibodies (scFv-cDNAs); (4) ligating the scFv-cDNAs into a phagemid vector; (5) transforming a host bacterium with the phagemid vector; (6) isolating phages that bind to the cell population(s); (7) excising the scFv-encoding cDNA from the phages obtained in step (6) and ligating the cDNA into a psi-negative retroviral Env expression vector, comprising an env gene, to produce an Env-scFv expression vector; (8) transforming the Env-scFv expression vector into a packaging cell; and (9) isolating the retroviral vectors secreted by the packaging cell.

Dornburg discloses a retroviral particle having a targeting peptide fused to the envelope protein of the retroviral vector. As discussed above, Dornburg does not teach any method for producing a cell-specific retroviral vector using unknown antibodies. More specifically, Dornburg says nothing about immunizing a mammal, isolating RNA, producing a cDNA, ligating the cDNA into a phagemid vector, isolating phages that bind to the cell populations, transforming an Env-scFv expression vector into a packaging cell, and isolating the retroviral vectors secreted by the packaging cell.

The remaining references are similarly lacking. While June and Colcher suggest immunizing an animal with a whole cell or a membrane-enriched fraction, respectively, neither reference discloses any steps for making any sort of retroviral vector, let alone the steps required by Applicants' present claims. Novotny teaches the production of immune libraries by amplifying RNA from IgG producing B cells but, like June and Colcher, fails to suggest several of the steps required by Applicants' claims. For example, nothing in Novotny suggests ligating scFv-cDNAs into a phagemid vector, transforming a host bacterium with the phagemid vector, isolating phages, excising scFv-encoding cDNA from phages, or producing a cell-specific retroviral vector. Thus, even when combined, Dornburg, June, Colcher and Novotny do not provide all the affirmative limitations, as recited in the presently pending claims. Accordingly, Applicants submit that the references do not support a *prima facie* case of obviousness under the provisions of 35 U.S.C. § 103 and respectfully request withdrawal of the rejection.

Other Matters

The Examiner indicates that the formal drawings supplied by the Applicants with the Amendment filed August 11, 2003, have not been matched with this case, and requests another set of drawings. Applicants submit herewith another set of formal drawings.

Applicants request that all claims be allowed. Enclosed is a Petition for Extension of Time along with the required fee. Please apply any other charges or credits to Deposit Account 06-1050.

Respectfully submitted,

Date: 21 APRIL 2004

Rolando Medina, Ph.D., J.D.
Reg. No. 54,756

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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